THIS OPINION WAS NOT WRITTEN FOR PUBLICATION

The opinion in support of the decision being entered today (1) was not written for publication in a law journal and (2) is not binding precedent of the Board.

Paper No. 22

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte ANTHONY L. FITZHUGH
and RHONE K. AKEE

Appeal No. 95-2257
Application 07/977,008[1]

HEARD: February 6, 1997

Before GARRIS, WARREN and THIERSTEIN, Administrative Patent Judges.

GARRIS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on an appeal from the final rejection of claims 1 through 9, which are all of the claims in the application.

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[1] Application for patent filed November 16, 1992.

The subject matter on appeal relates to a method for resolving a mixture of (6R,6S) diastereomers of 5,6,7,8-tetrahydrofolic acid derivatives. The method comprises (a) α-esterifying the derivatives so as to produce a (6R,6S) monoester having a protecting group, (b) separating the (6S) and (6R) form of the α-monoester by chromatography or fractional crystallization and (c) deprotecting the separated (6S) or (6R) α-monoester to thereby produce pure (6S)- or (6R)-5,6,7,8-tetrahydrofolic acid derivatives. The appealed subject matter also relates to a method for separating α-monoesters of a (6R,6S) mixture of 5,6,7,8-tetrahydrofolic acid derivatives by subjecting a mixture of (6R,6S)-5,6,7,8-tetrahydrofolate to high pressure liquid chromatography, column chromatography or fractional crystallization to thereby separate the mixture into 100% diastereomerically pure (6R)- and 100% diastereomerically pure (6S)-5,6,7,8-tetrahydrofolate. This appealed subject matter is adequately illustrated by independent claims 1 and 9,[2] a reproduction of which taken from the main brief is appended to this decision.

[2] Claim 9 contains a minor informality which is deserving of correction. On the fifth line from the bottom of claim 9 the expression "$_{C1}$ - C_8" should read --C_1 - C_8 --. This correction should be made in any further prosecution that may occur.

The following references are applied by the examiner in the rejections before us:

Wood et ~~al.~~ (Wood)	4,959,472	Sep. 25, 1990
Fitzhugh	5,153,309	Oct. 6, 1992

Kaufman et al. (Kaufman), "Chromatographic Separation of the Diastereoisomers of dl, L-5, 10-Methylenetetrahydrofolate," The Journal of Biological Chemistry, Vol. 238, No. 4, pp. 1498-1500, April 1963.

Fitzhugh et al., (Fitzhugh), "A New and Facile Synthetic Route to N^5-Formyl Tetrahydropteroylpoly-L-Glutamates," Bioorganic & Medicinal Chemistry Letters, Vol. 1, No. 3, pp. 155-158, 1991.

Wainer et al. (Wainer), "Direct Resolution of Stereoisomers of leucovorin and 5-methyltetrahydrofolate Using a Bovine Serum Albumin High-Performance Liquid Chromatographic Chiral Stationary Phase Coupled to an Achiral Phenyl Column, Journal of Chromatography, 424, pp. 158-162, 1988.

Claims 1 through 9 stand rejected under the first and second paragraphs of 35 U.S.C. § 112 "as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention" (main answer, page 13).

Claims 1 through 8 stand rejected under 35 U.S.C. § 102(b) as being anticipated by or under 35 U.S.C. § 103 as being obvious over the Fitzhugh patent.

Claims 1 through 8 stand rejected under the judicially created doctrine of obviousness-type double patenting as being obvious over claims 1 through 10 of the Fitzhugh patent.

Claims 1 through 9 stand rejected under 35 U.S.C. § 102(b) or (f) as being anticipated by or under 35 U.S.C. § 103 as being obvious over the Fitzhugh article.

Claim 9 stands rejected under 35 U.S.C. § 103 as being obvious over Wood in view of the Fitzhugh patent.

Finally, claim 9 stands rejected under 35 U.S.C. § 103 as being obvious over Kaufman or Wainer in view of the Fitzhugh article.

For a complete exposition of the opposing viewpoints expressed by the appellants and the examiner concerning the above-noted rejections, we refer to the main and reply briefs and to the main and supplemental answers.

Opinion

We cannot sustain any of the rejections advanced by the examiner on this appeal.

The Section 112 Rejections

On pages 24 through 27 of the main brief, the appellants have set forth their reasons for considering the examiner's Section 112 rejections to be improper. We find these reasons

to be well taken and adopt them as our own. We add the following comments for emphasis and completeness.

It is the examiner's position that the here-claimed step of separating α-monoesters by chromatography or fractional crystallization renders the claims in violation of the first paragraph of 35 U.S.C. § 112. For example, the examiner contends that "[n]o enablement for fractional crystallization is described in the instant specification" (main answer, page 14). The examiner appreciates that page 6 of the appellants' specification refers to a publication by Mueller which describes a prior art fractional crystallization method for separating diastereomers (also see lines 1 through 6 on specification page 18 wherein the appellants teach that the separation of their α-monoesters "can be carried out by any of the known methods in the art for the resolution of diastereomers, such as, high pressure liquid chromatography, column chromatography or fractional crystallization"). Nevertheless, the examiner urges that "the undescribed method may not work" (main answer, page 14).

As correctly pointed out by the appellants, it is the examiner's burden to advance acceptable reasoning inconsistent with enablement. In re Strahilevitz, 668 F.2d 1229, 1232, 212 USPQ 561, 563 (CCPA 1982). From our perspective, the examiner

has not provided convincing reasons for doubting enablement in this case. It is appropriate to emphasize that the record on this appeal evinces that methods for separating diastereomers by chromatography and fractional crystallization are well known in the prior art. We find no persuasive support for the examiner's position that the here-claimed step of separating (6S) and (6R) α-monoesters by chromatography or fractional crystallization could not be practiced by one having ordinary skill in the art without undue experimentation. Therefore, we accept (as we must) the appellants' aforequoted teaching that the here-claimed separating step "can be carried out by any of the known methods in the art for the resolution of diastereomers."

For the above-stated reasons and for the reasons expressed in the main brief, the Section 112, first and second paragraphs, rejections of claims 1 through 9 cannot be sustained.

The Section 102/Section 103 and Double Patenting Rejections over the Fitzhugh patent

It is well settled that anticipation is established only when a single prior art reference discloses, expressly or under principles of inherency, each and every element of a claimed invention. Kalman v. Kimberly-Clark Corp., 713 F.2d 760, 771, 218 USPQ 781, 789 (Fed. Cir. 1983), cert. denied, 465 U.S. 1026 (1984) (and overruled in part on another issue) 775 F.2d 1107, 227 USPQ 577 (Fed. Cir. 1985). Unquestionably, the Fitzhugh

patent contains no express teaching of the (6S) and (6R) separating step claimed by the appellants. Further, it is quite clear that the here-claimed separating step is not inherently practiced in the method of the Fitzhugh patent. In this regard, the appellants have correctly explained that the resolution step in the patent method effects separation of α-monoesterified from γ-monoesterified product but does not effect separation of the (6R) and (6S) forms of the monoester. This is most clearly illustrated by Example 1 of the Fitzhugh patent in which the α-monoester product is expressly disclosed as including the (6R) and (6S) forms (cf., lines 10 and 11 with lines 24 through 28 in column 8).

Under the foregoing circumstances, it is apparent that we cannot sustain the examiner's Section 102 rejection of claims 1 through 8 as being anticipated by Fitzhugh.

The corresponding Section 103 rejection of these claims also cannot be sustained. Although the prior art recognizes the desirability of resolving (6R,6S) mixtures of hydrofolic acid derivatives, the Fitzhugh patent contains no teaching or suggestion of doing so by separating the (6R) and (6S) forms of the corresponding α-monoester. Only the appellants' own disclosure

teaches this separating step. It follows that the examiner's obviousness conclusion must be based upon the application of impermissible hindsight derived from the appellants' disclosure rather than some teaching, suggestion or incentive derived from the applied prior art.

Because the Fitzhugh patent as a whole fails to support the Section 103 rejection of appealed claims 1 through 8, a fortiori, the claims of this patent fail to support the obviousness-type double patenting rejection of appealed claims 1 through 8. Accordingly, this obviousness-type double patenting rejection cannot be sustained for the reasons expressed above.

The Section 102/Section 103 Rejections over the Fitzhugh Article

The Fitzhugh article is closely related in subject matter, and shares the same deficiencies as, the above-discussed Fitzhugh patent. Specifically, the Fitzhugh article contains no express teaching of separating the (6S) and (6R) forms of the α-monoester under consideration and would not have inherently effected this separation for the reasons explained by the appellants in their briefs. Additionally, the Fitzhugh article like the Fitzhugh patent simply contains no teaching, suggestion or incentive which

supports the examiner's conclusion of obviousness viz-à-viz the here-claimed separating step. As a consequence, we cannot sustain the examiner's rejection of claims 1 through 9 under Section 102(b) or (f) as being anticipated by, or under Section 103 as being obvious over, the Fitzhugh article.

The Section 103 Rejections over Wood in view of the Fitzhugh Patent and over Kaufman or Wainer in view of the Fitzhugh Article

In the rejections under consideration, the examiner has not relied upon the Wood, Kaufman or Wainer references for supplying the aforementioned deficiencies of the Fitzhugh patent and the Fitzhugh article. Moreover, our study of Wood, Kaufman and Wainer does not reveal that these references supply the deficiencies. It follows that we also cannot sustain the examiner's Section 103 rejections of claim 9 as being obvious over Wood in view of the Fitzhugh patent and over Kaufman or Wainer in view of the Fitzhugh article.

Summary

For the reasons set forth above and in the briefs, we have not sustained any of the rejections advanced by the examiner on this appeal.

The decision of the examiner is reversed.

REVERSED

BRADLEY R. GARRIS
Administrative Patent Judge

CHARLES F. WARREN
Administrative Patent Judge

JOAN THIERSTEIN
Administrative Patent Judge

BOARD OF PATENT APPEALS AND INTERFERENCES

Appeal No. 95-2257
Application 07/977,008

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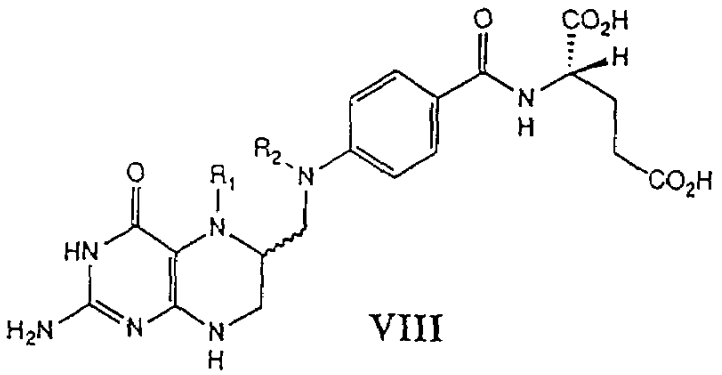
APPENDIX

CLAIMS 1 and 9

1. A method for resolving a mixture of (6R,6S)-diastereomers of 5,6,7,8-tetrahydrofolic acid derivative which comprises:

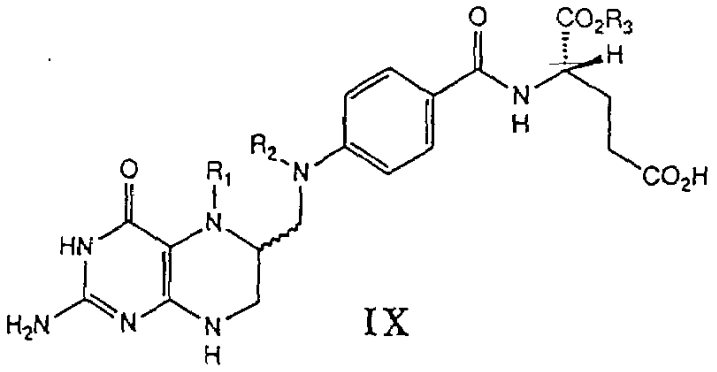
(a) α-esterifying a (6R,6S)-5,6,7,8-tetrahydrofolic acid derivative according to formula VIII:



VIII

wherein R1 is C_1 - C_6 alkyl, C_1 - C_6 alkyl carbonyl, C_1 - C_6 alkoxy carbonyl, or -CHO, wherein said alkyl, alkyl carbonyl, and alkoxy carbonyl may be substituted with halogen, C_1 - C_6 alkoxy, or phenyl; R_2 is H, C_1 - C_6 alkyl, C_1 - C_6 alkyl carbonyl, C_1 -C_6 alkoxy carbonyl, or -CHO, wherein said alkyl, alkyl carbonyl, and alkoxy carbonyl may be substituted with halogen, C_1 - C_6 alkoxy, or phenyl; or R_1 and R_2 join together to form a one carbon bridge between the 5 and 10 positions; so as to produce a (6R,6S) monoester according to formula IX:

APPENDIX



IX

wherein R_1 and R_2 are as defined in formula VIII and R_3 is a protecting group;

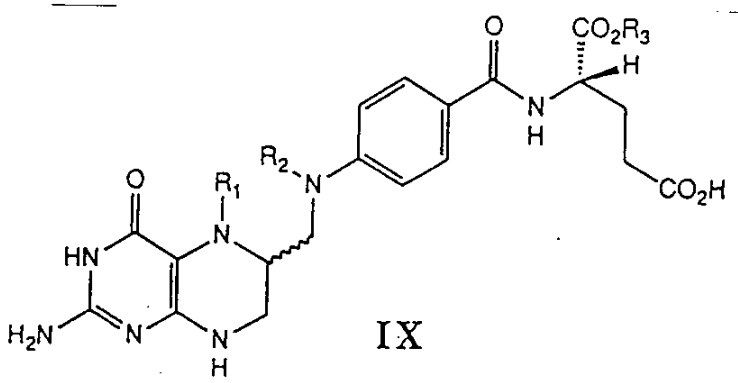
(b) separating the (6S) and (6R) form of said α-monoester by chromatography or fractional crystallization; and

(c) deprotecting said separated (6S) or (6R) α-monoester, thereby producing pure (6S)- or (6R)-5,6,7,8-tetrahydrofolic acid derivative.

9. A method for separating α-monoesters of a (6R,6S) mixture of 5,6,7,8-tetrahydrofolic acid derivatives, which comprises:

subjecting a mixture of (6R,6S)-5,6,7,8-tetrahydrofolate represented by formula IX to high pressure liquid chromatography, column chromatography or fractional crystallization, thereby

separating said mixture into 100% diastereomerically pure (6R)- and 100% diastereomerically pure (6S)-5,6,7,8-tetrahydrofolate:



IX

wherein R_1 is C_1 - C_6 alkyl, C_1 - C_6 alkyl carbonyl, C_1 - C_6 alkoxy carbonyl, or -CHO, wherein said alkyl, alkyl carbonyl, and alkoxy carbonyl may be substituted with halogen, C_1 - C_6 alkoxy, or phenyl; R_2 is H, C_1 - C_6 alkyl, C_1 - C_6 alkyl carbonyl, C_1 -C_6 alkoxy carbonyl, or -CHO, wherein said alkyl, alkyl carbonyl, and alkoxy carbonyl may be substituted with halogen, C_1 - C_6 alkoxy, or phenyl; or R_1 and R_2 join together to form a one carbon bridge between the 5 and 10 positions; and R_3 is $_{C1}$ - C_8 alkyl, C_5 - C_6 cycloalkyl, substituted C_5 - C_6 cycloalkyl, C_6 - C_{10} aryl (phenyl and naphthyl), substituted C_6 - C_{10} aryl, C_6 - C_{10} aryl C_1 - C_8 alkyl, substituted C_6 - C_{10} aryl C_1 - C_8 alkyl, diphenylmethyl, substituted diphenyl methyl and trialkylsilyl.